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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/761,481	01/20/2004	Nozer M. Mehta	P/546-280	2921

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OSTROLENK FABER LLP
1180 AVENUE OF THE AMERICAS
NEW YORK, NY 10036-8403

EXAMINER	
RUSSEL, JEFFREY E	
ART UNIT	PAPER NUMBER
1654	
MAIL DATE	DELIVERY MODE
08/24/2011	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/761,481	MEHTA ET AL.	
	Examiner	Art Unit	
	Jeffrey E. Russel	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 July 2011*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *1-3,5,6,8,11-15,17-37,39-46,48-53,55,57-60 and 63* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-3,5,6,8,11-15,17-37,39-46,48-53,55,57-60 and 63* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *20110505*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

1. The effective filing date of instant claims 1-3, 5, 6, 8, 11-15, 17-37, 39-46, 48-53, 55, 57-60, and 63 is January 21, 2003, the filing date of provisional application 60/441,856. Instant claims 1-3, 5, 6, 8, 11-15, 17-37, 39-46, 48-53, 55, 57-60, and 63 are deemed to be entitled under 35 U.S.C. 119(e) to the benefit of the filing date of the provisional application because the provisional application, under the test of 35 U.S.C. 112, first paragraph, discloses the claimed subject matter.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. Claims 1-3, 5, 6, 8, 12-15, 17-37, 39-41, 43-46, 49-51, 55, 57-59, and 63 are rejected under 35 U.S.C. 103(a) as being obvious over Stern et al (U.S. Patent No. 6,086,918) in view of Habener (U.S. Patent No. 5,120,712), Mandic (U.S. Patent Application Publication 2003/0104981), or Barbier et al (U.S. Patent No. 6,110,892). Stern et al teach oral administration of peptides such as insulin and parathyroid hormone using a carrier comprising a pH-lowering agent, an absorption enhancer, a non-physiologically active protein, a gelatin capsule, and an enteric coating. See, e.g., column 6, line 1 - column 12, line 10, and claims 1-55. Stern et al do not teach peptides which are GLP-1 analogs which are amidated at their C-terminus, insulin analogs which are amidated at their C-terminus, or PTH analogs which are amidated at their C-terminus. Habener teaches GLP-1 analogs which can be C-terminally amidated. See, e.g., column 4, lines 14-25, and claims 1 and 4. Mandic teaches insulin analogs in which the carboxy terminus of the B chain is amidated. The insulin analogs have enhanced stability to insulin-degrading enzyme. See, e.g., the Abstract and Figures 1-2. Barbier et al teach the human parathyroid hormone derivative hPTH(1-31)NH_2, and teach that the derivative can be

administered orally. See, e.g., column 2, lines 26-44, and column 14, lines 59-62. It would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to use the specific peptides of Habener, Mandic and Barbier et al in the oral administration compositions of Stern et al because the oral administration compositions of Stern et al have general applicability to any peptide and because it would be desirable to be able to administer orally the peptides of Habener, Mandic, and Barbier et al, because oral administration is easier for the patient. Applicants' claims would have been prima facie obvious at the time the invention was made because applying Stern et al's known and generally applicable technique, i.e. of combining peptides with a pH-lowering agent, an absorption enhancer, a non-physiologically active protein, a gelatin capsule, and an enteric coating so that the peptides can be administered orally, to the known and specific peptides of Habener, Mandic, and Barbier et al, with only the expected result that the known and specific peptides of Habener, Mandic, and Barbier et al, can be administered orally, is prima facie obvious. See KSR International Co. v. Teleflex Inc., 82 USPQ2d 1385 (S. Ct. 2007). With respect to instant claim 5, process limitations do not impart novelty and unobviousness to product-by-process claims where the product is otherwise anticipated by or obvious over the prior art. With respect to instant claims 6 and 49, each of the GLP-1 analogs of Habener, the insulin analogs of Mandic, and the hPTH analogs of Barbier et al comprises Gln and/or Asn residues, and therefore comprises amino acids containing amidated side chains.

4. Claims 5 and 48 are rejected under 35 U.S.C. 103(a) as being obvious over Stern et al (U.S. Patent No. 6,086,918) in view of Habener (U.S. Patent No. 5,120,712), Mandic (U.S. Patent Application Publication 2003/0104981), or Barbier et al (U.S. Patent No. 6,110,892) as

applied against claims 1-3, 5, 6, 8, 12-15, 17-37, 39-41, 43-46, 49-51, 55, 57-59, and 63 above, and further in view of Stern et al (U.S. Patent No. 5,912,014). Habener, Mandic, and Barbier et al teach known and specific peptides which are amidated at their C-termini, but do not teach synthesizing these peptides by forming glycine-extended precursors and then converting the glycine residue to a C-terminal amide group. Stern et al '014 teaches salmon calcitonin made with a C-terminal glycine extension which is enzymatically converted to an amide group. See, e.g., column 5, lines 12-23. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to form the known and specific peptides of Habener, Mandic, and Barbier et al for use in the oral administration compositions of Stern et al '918 by synthesizing the peptides as glycine-extended precursors and then converting the glycine residue to a C-terminal amide group, because Stern et al '014 teach that this is a known reaction technique for forming a C-terminally amidated peptide, and because the particular method of synthesizing a peptide would not have been expected to affect the in vivo activity of the peptide.

5. Claims 1-3, 5, 6, 8, 11-15, 17-37, 39-41, 43-46, 49-53, 55, 57-59, and 63 are rejected under 35 U.S.C. 103(a) as being obvious over the WO Patent Application 02/043767 in view of Habener (U.S. Patent No. 5,120,712), Mandic (U.S. Patent Application Publication 2003/0104981), or Barbier et al (U.S. Patent No. 6,110,892). The WO Patent Application '767 teaches oral administration of peptides such as insulin, salmon calcitonin, parathyroid hormone, lhrf, and GLP-1 linked to a membrane translocator using a carrier comprising a pH-lowering agent, a protease inhibitor, an absorption enhancer, a non-physiologically active peptide, a gelatin capsule, and an enteric coating. See, e.g., page 17, lines 13-22, page 18, lines 10-27, page 20, lines 11-29, and claims 1-57. [Note that the WO Patent Application '767 does not

designate the US, and therefore is not available as prior art under 35 U.S.C. 102(e).] The WO Patent Application '767 does not teach peptides which are GLP-1 analogs which are amidated at their C-terminus, insulin analogs which are amidated at their C-terminus, or PTH analogs which are amidated at their C-terminus. Habener teaches GLP-1 analogs which can be C-terminally amidated. See, e.g., column 4, lines 14-25, and claims 1 and 4. Mandic teaches insulin analogs in which the carboxy terminus of the B chain is amidated. The insulin analogs have enhanced stability to insulin-degrading enzyme. See, e.g., the Abstract and Figures 1-2. Barbier et al teach the human parathyroid hormone derivative hPTH(1-31)NH_2, and teach that the derivative can be administered orally. See, e.g., column 2, lines 26-44, and column 14, lines 59-62. It would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to use the specific peptides of Habener, Mandic and Barbier et al in the oral administration compositions of the WO Patent Application '767 because the oral administration compositions have general applicability to any peptide and because it would be desirable to be able to administer orally the peptides of Habener, Mandic and Barbier et al because oral administration is easier for the patient. Applicants' claims would have been prima facie obvious at the time the invention was made because applying the WO Patent Application '767's known and generally applicable technique, i.e. of combining peptides with a pH-lowering agent, a protease inhibitor, an absorption enhancer, a non-physiologically active peptide, a gelatin capsule, and an enteric coating so that the peptides can be administered orally, to the known and specific peptides of Habener, Mandic and Barbier et al, with only the expected result that the known and specific peptides of Habener, Mandic and Barbier et al can be administered orally, is prima facie obvious. See KSR International Co. v. Teleflex Inc., 82 USPQ2d 1385 (S. Ct. 2007). With respect to

instant claim 5, process limitations do not impart novelty and unobviousness to product-by-process claims where the product is otherwise anticipated by or obvious over the prior art. With respect to instant claims 6 and 49, each of the GLP-1 analogs of Habener, the insulin analogs of Mandic, and the hPTH analogs of Barbier et al comprises Gln and/or Asn residues, and therefore comprises amino acids containing amidated side chains.

6. Claims 5 and 48 are rejected under 35 U.S.C. 103(a) as being obvious over the WO Patent Application 02/043767 in view of Habener (U.S. Patent No. 5,120,712), Mandic (U.S. Patent Application Publication 2003/0104981), or Barbier et al (U.S. Patent No. 6,110,892) as applied against claims 1-3, 5, 6, 8, 11-15, 17-37, 39-41, 43-46, 49-53, 55, 57-59, and 63 above, and further in view of Stern et al (U.S. Patent No. 5,912,014). Habener, Mandic and Barbier et al teach known and specific peptides which are amidated at their C-termini, but do not teach synthesizing these peptides by forming glycine-extended precursors and then converting the glycine residue to a C-terminal amide group. Stern et al '014 teaches salmon calcitonin made with a C-terminal glycine extension which is enzymatically converted to an amide group. See, e.g., column 5, lines 12-23. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to form the known and specific peptides of Habener, Mandic and Barbier et al for use in the oral administration compositions of the WO Patent Application '767 by synthesizing the peptides as glycine-extended precursors and then converting the glycine residue to a C-terminal amide group, because Stern et al '014 teaches that this is a known reaction technique for forming a C-terminally amidated peptide, and because the particular method of synthesizing a peptide would not have been expected to affect the in vivo activity of the peptide.

7. Claims 1, 5, 6, 17-19, 40, and 41 are rejected under 35 U.S.C. 102(b) as being anticipated by the Neugebauer et al article (Biochemistry, Vol. 34, pages 8835-8842). The Neugebauer et al article teaches a composition comprising hPTH(1-31)NH_2 combined with palmitoyloleoyl-phosphatidylserine vesicles in phosphate-buffered solution. See, e.g., page 8836, column 1, second full paragraph, and column 2, second paragraph; page 8839, Figure 7 and paragraph bridging columns 1 and 2. The palmitoyloleoyl-phosphatidylserine present in the vesicles of the Neugebauer et al article corresponds to Applicants' absorption enhancer. Note that an intended use limitation, e.g., "orally delivered", does not impart patentability to product claims where the product is otherwise anticipated by the prior art. Because the Neugebauer et al article teaches the only components specified in Applicants' claims, i.e. hPTH(1-31) amidated at its C-terminus and a phospholipid, inherently the composition of the Neugebauer et al article will provide enhanced bioavailability of the amidated peptide when it is orally delivered to the same extent claimed by Applicants. Sufficient evidence of similarity is deemed to be present between the compositions of the Neugebauer et al article and Applicants' claimed compositions to shift the burden to Applicants to provide evidence that the claimed compositions are unobviously different than those of the Neugebauer et al article. With respect to instant claim 5, process limitations do not impart novelty and unobviousness to product-by-process claims where the product is otherwise anticipated by or obvious over the prior art. With respect to instant claim 6, hPTH(1-31)NH_2 comprises Gln and Asn residues at positions 6, 10, 16, and 29, and thus comprises amino acids containing amidated side chains. With respect to instant claim 40, hPTH(1-31)NH_2 is an analog of human parathyroid hormone.

8. Applicant's arguments filed July 27, 2011 have been fully considered but they are not

persuasive.

The obviousness rejections based upon Stern et al (U.S. Patent No. 6,086,918) or the WO Patent Application 02/043767, in view of Habener (U.S. Patent No. 5,120,712), Mandic (U.S. Patent Application Publication 2003/0104981), or Barbier et al (U.S. Patent No. 6,110,892), are maintained for the reasons of record. The examiner agrees that Habener, Mandic, and Barbier et al teach non-amidated peptides as well as amidated peptides. The examiner's position is that it would have been prima facie obvious to administer any of these peptides, regardless of whether they are C-terminally amidated, using the oral administration compositions of Stern et al and the WO Patent Application '767. It would have been expected that such compositions would be effective upon oral administration, because Stern et al and the WO Patent Application '767 teaches that their oral administration compositions permit effective oral administration of peptide therapeutic agents regardless of the particular identity of the peptide therapeutic agents. The examiner agrees that none of the secondary references disclose or suggest the selective use of C-terminal amidated peptides in the oral delivery system of the primary references. However, this argument is not convincing because the secondary references are not applied individually but rather are applied in combination with Stern et al and with the WO Patent Application '767, and the determination of obviousness is based upon consideration of the prior art as a whole, not upon individual references. Of course, it also is not a requirement for prima facie obviousness that any of the applied references, including the secondary references, contain an express written motivation to combine the references. See MPEP 2145(X)(A). To the extent that Applicants are arguing that C-terminally amidated peptides have unexpectedly higher therapeutic activity upon oral administration than do the corresponding non-amidated peptides, Applicants have not

submitted evidence which demonstrates this assertion either for peptides in general or for the particular peptides taught by Habener, Mandic, and Barbier et al.

The examiner agrees that the obviousness rejections of claims 5 and 48 will stand or fall with the corresponding obviousness rejections of the independent claims.

The anticipation rejection over the Neugebauer et al article (Biochemistry, Vol. 34, pages 8835-8842) is maintained for the reasons of record. Applicants point out that palmitoyloleoyl-phosphatidylserine is included in the compositions of the Neugebauer et al article for purposes of studying helix structure, not to enhance oral delivery. However, at issue are product claims, and the intent behind the prior art teaching of the product does not avoid an anticipation rejection where the prior art teaches the claimed product. Applicants contend that "oral pharmaceutical composition" is a structural limitation and is intended to cover tablets, capsules, and other oral dosage forms. To the extent that "oral pharmaceutical composition" is a structural limitation, this limitation does embrace the vesicles of the Neugebauer et al article as suitable oral administration forms. See, e.g., Bolcsak et al (U.S. Patent Number 5,100,062) at column 15, lines 50-53; and Eustache et al (U.S. Patent Application Publication 2003/0134896) at paragraph [0123]; which teach that vesicles are suitable oral administration forms. The examiner agrees that claims limited to tablet or capsule administration forms would not be anticipated by or obvious over the Neugebauer et al article.

9. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey E. Russel at telephone number (571) 272-0969. The examiner can normally be reached on Monday-Thursday from 8:00 A.M. to 5:30 P.M. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Cecilia Tsang can be reached at (571) 272-0562. The fax number for formal communications to be entered into the record is (571) 273-8300; for informal communications such as proposed amendments, the fax number (571) 273-0969 can be used. The telephone number for the Technology Center 1600 receptionist is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Jeffrey E. Russel/
Primary Examiner, Art Unit 1654

JRussel
August 23, 2011